Lymphatic and Local Spread of T1 and T2 Pancreatic Cancer

A Study of Autopsy Material

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Eight autopsy cases of pancreatic cancer (duct cell adenocarcinoma) with T1 and T2 primary tumors were studied histologically to examine the exact extent of lymphatic and local spread. Six of them had microscopic metastasis in grossly negative lymph nodes near the primary tumor. In addition, four of them had a few metastatic nodes in the para-aortic region. In cases with lymphatic metastases, the extent of cancer infiltration within lymphatic vessels, nerves, and/or connective tissues was almost the same as that of lymph node metastasis. Major vascular involvement was found in four cases. There was no case in which multicentricity or marked intraductal spread of cancer cells was observed in the pancreas. It has been suggested that most of T1 and T2 pancreatic cancers have a fairly widespread microscopic extension, although extremely small T1 cancers have a very limited extension.

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ALMOST ALL EFFORTS for radical treatment of exocrine pancreatic cancer have failed to obtain a long-term survival of patients with this formidable disease.[1–4] Besides a marked difficulty with early detection of the cancer, one of the most important reasons for this failure is a remarkable tendency to invasion and metastasis of duct cell adenocarcinoma of the pancreas: high incidence of hematogenous spread, peritoneal dissemination, widespread lymphatic metastases, and extensive local invasion, especially into the neighboring major vessels. Hematogenous and peritoneal spreads are both beyond the reach of surgical treatment, whereas lymphatic metastases and local invasion can be eradicated surgically, at least theoretically, as long as the extension of the tumor is limited within certain areas.

Fortner[5] reported regional pancreatectomy, including removal of the primary lymphatic drainage of the pancreas, and resection of the portal vein (Type I procedure) and hepatic artery or arteries, celiac axis, or superior mesenteric artery (Type II procedure). He courageously performed these procedures for advanced pancreatic cancers, most of which had a tumor of more than 6 cm in diameter or with extensive direct extension to contiguous structures. However, even his procedures have failed so far to obtain a remarkable improvement in long-term survival rates,[6] which would suggest that these advanced cancers of the pancreas might already have had cancer extension beyond the limit of surgical management.

It is an interesting and crucial problem where cancer spread actually takes place in pancreatic cancer of small size and with macroscopically localized extension. By histologic examination of autopsy material, we performed the present study to determine the exact extent of lymphatic metastasis and local spread in patients with small and macroscopically localized pancreatic cancer (duct cell adenocarcinoma). Local spread was studied in terms of cancer infiltration within lymphatic vessels, nerves, and loose connective tissues, which we provisionally call "interstitial invasion" collectively, as well as invasion into the major vascular structures. We also searched for multiple cancerous foci within the pancreas and intraductal spread of cancer cells in relation to the problem of whether total or partial pancreatectomy should be done as part of a radical resection of pancreatic cancer.

Materials and Methods

We used the autopsy materials at Tokyo Metropolitan Geriatric Hospital, Tokyo, during 1980–1983. Eight cases with gross primary tumor localized in the pancreas and its neighboring tissues were selected out of 54 cases of unresected duct cell adenocarcinoma. No evidence of pri-

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TABLE 1. *Outlines of Eight Autopsy Cases with T1 and T2 Pancreatic Cancer*

Primary Tumor	Case No.	Age, Sex	Site of Primary Tumor	Macroscopic Size (cm)	Direct Extension	Hematogenous Metastasis	Peritoneal Seeding
T1	1	84, F	Body	0.8 × 0.7	—	—	—
	2	79, M	Tail	1.2 × 1.2	—	—	—
	3	80, M	Head	0.4 × 0.3	—	—	—
	4	76, F	Body	0.8 × 0.8	—	—	—
T2	5	51, M	Head	3.0 × 3.0	Bile duct, duodenum	—	—
	6	82, M	Head	3.5 × 3.5	Bile duct, duodenum	Liver	—
	7	72, F	Head	3.0 × 3.5	Bile duct, duodenum	—	—
	8	74, F	Head	4.5 × 5.5	Bile duct, duodenum	—	—

mary cancer in other organs was found in these eight cases. Tumors of four cases belonged to T1 ("no direct extension of the primary tumor beyond the pancreas") and those of four cases of T2 ("limited direct extension to the duodenum, bile ducts, or stomach") according to the classification of the American Joint Committee on Cancer (AJCC)[7] (Table 1). None of the eight cases showed macroscopically detectable lymph node metastases. Hematogenous metastases and peritoneal seeding were absent both macroscopically and microscopically in all but one case with T2 tumor and liver metastasis. Thus, if the surgical-evaluative staging of the AJCC were applied on the macroscopic findings, seven of our cases would have been in Stage I (T1–2, N0, M0) and the other one in Stage IV (T2, N0, M1).

Serial step sectioning, about 300 histologic sections per case, was used to examine the entire pancreas and its surrounding structures including the retroperitoneum and radix of the mesentery (Fig. 1). All histologic sections were stained with hematoxylin and eosin, and elastica-Masson staining was used for some of them.

Regional lymph nodes of the pancreas were divided into 11 groups, as shown in Figure 2. Mediastinal and cervical nodes were also examined histologically.

Results

Lymph Node Metastases

Six of the eight cases had microscopic lymph node metastases (Table 2).

A T1 cancer in the body (Case 1) had three positive nodes out of 168 nodes examined: one node in each of the superior body, juxta-aortic, and para-aortic groups. Another T1 cancer in the tail (Case 2) had one metastatic node in the upper body group out of 150 nodes. The other two T1 tumors (Cases 3 and 4), 0.4 and 0.8 cm in diameter and located in the head and body, respectively, had no lymphatic metastasis in any of 133 to 159 nodes examined.

All four cases with T2 tumors (Cases 5–8) in the head of the pancreas had lymphatic metastases to nodes of the posterior pancreaticoduodenal, inferior head, and juxta-aortic group; three of them to nodes of the para-aortic group; two cases to nodes of the anterior pancreaticoduodenal and superior head group; and one case to a node of the perigastric group. The total number of involved nodes in these four T2 cancers was 11 to 26 of 97 to 240.

Involvement of para-aortic nodes in one T1 tumor

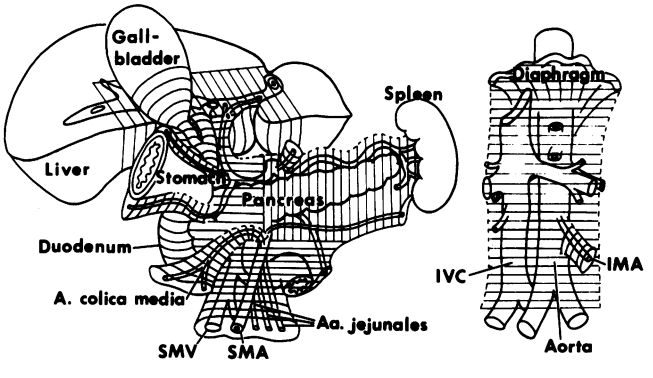


FIG. 1. Schematic drawing of serial step sectioning of the pancreas and its surrounding structures. IMA = inferior mesenteric artery. IVC = inferior vena cava. SMA = superior mesenteric artery. SMV = superior mesenteric vein.

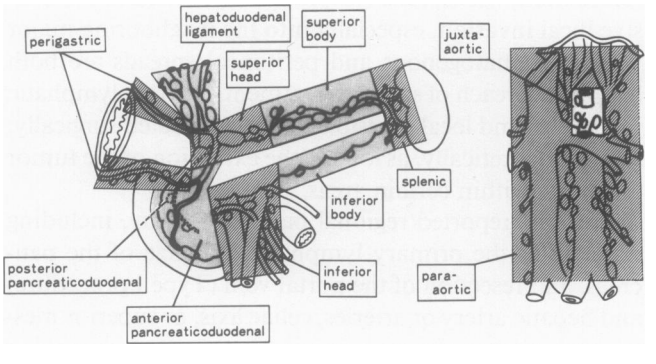


FIG. 2. Grouping of regional lymph nodes of the pancreas. 1 = perigastric group. 2 = anterior pancreaticoduodenal group. 3 = posterior pancreaticoduodenal group. 4 = superior head group. 5 = superior body group. 6 = inferior head group. 7 = inferior body group. 8 = splenic group. 9 = hepatoduodenal ligament group. 10 = juxta-aortic group. 11 = para-aortic group.

TABLE 2. *Lymph Node Metastasis of T1 and T2 Pancreatic Cancer*

Lymph Node/ Case No.		Peri-gastric	Anterior Pancreatico-duodenal	Posterior Pancreatico-duodenal	Superior Head	Superior Body	Inferior Head	Inferior Body	Splenic	Hepato-duodenal Ligament	Juxta-aortic	Para-aortic	Mediastinal and Cervical	Total
T1	1	0/17*	0/2	0/5	0/2	1/29	0/11	0/4	0/5	0/4	1/10	1/70	0/9	3/168
	2	0/19	0/2	0/7	0/6	1/17	0/17	0/3	0/4	0/6	0/7	0/58	0/4	1/150
	3	0/26	0/2	0/6	0/4	0/14	0/21	0/3	0/3	0/6	0/5	0/61	0/8	0/159
	4	0/14	0/3	0/6	0/3	0/10	0/16	0/2	0/5	0/8	0/5	0/57	0/4	0/133
T2	5	0/15	5/5	4/9	0/8	0/31	13/47	0/12	0/2	0/5	1/8	3/81	0/7	26/240
	6	0/10	0/2	6/7	1/8	3/11	2/19	0/2	0/9	0/10	1/5	0/53	0/5	13/141
	7	0/16	0/2	1/2	2/4	1/8	1/7	0/1	0/3	0/2	4/4	2/43	0/5	11/97
	8	1/31	1/2	4/15	0/8	0/29	4/26	0/1	0/2	0/8	1/3	3/57	0/9	14/191

* Number of involved nodes/total number of nodes examined.

(Case 1) and three T2 tumors (Cases 5, 7, and 8) was found in the areas around the origin of the bilateral renal artery (Fig. 3). In two T2 tumors (Cases 5 and 8), additional involvement was observed in nodes around the origin of the inferior mesenteric artery. The total number of positive para-aortic nodes in each of the four cases was only one to three out of 43 to 81.

Mediastinal and cervical nodes were not involved in any of the eight cases examined.

Cancer Infiltration within Lymphatics, Nerves, and Connective Tissues

All eight T1 and T2 cancers had "interstitial invasion," *i.e.*, cancer infiltration within lymphatic vessels, nerves, and/or connective tissues (Fig. 4, Table 3). As regards the range of "interstitial invasion" in cases with lymph node metastases, the invasion was almost invariably found in the regions where lymph node metastases were observed (Table 3, Fig. 5). In the para-aortic region, however, cancer cells in the form of "interstitial invasion" were found only around the base of the superior mesenteric artery, whereas the distribution of metastases to para-aortic lymph nodes ranged from the origin of the superior mesenteric artery to that of the inferior mesenteric artery (Fig. 3). "Interstitial invasion" in cases without lymph node metastases was limited to the areas around the main pancreatic tumors.

As shown in Table 3, there was some difference in the extent of infiltration within lymphatics and nerves. For example, Case 5 had remarkable infiltration within lymphatic vessels and only little infiltration within nerves, whereas Case 8 had the reverse relationship.

Invasion to the Major Vascular Structures

Table 4 shows the extent of invasion into the walls of major vessels, resection of which should become crucial in the surgical treatment of pancreatic cancer.

The portal vein system was directly involved in only one of the four T1 cancers, whereas three of the four T2 cancers had involvement of the portal vein system, especially of the superior mesenteric vein and/or main trunk of the portal vein. As for invasion to the arterial system, only one T2 cancer in the head of the pancreas involved the middle colic artery in addition to the portal vein and splenic vein.

Intraductal Spread and Multicentricity of Cancer

Neither marked intraductal spread nor multicentricity of cancer of the pancreas was observed in any case examined. There was no case in which intraluminal floating cancer cells were found far away from the primary tumor.

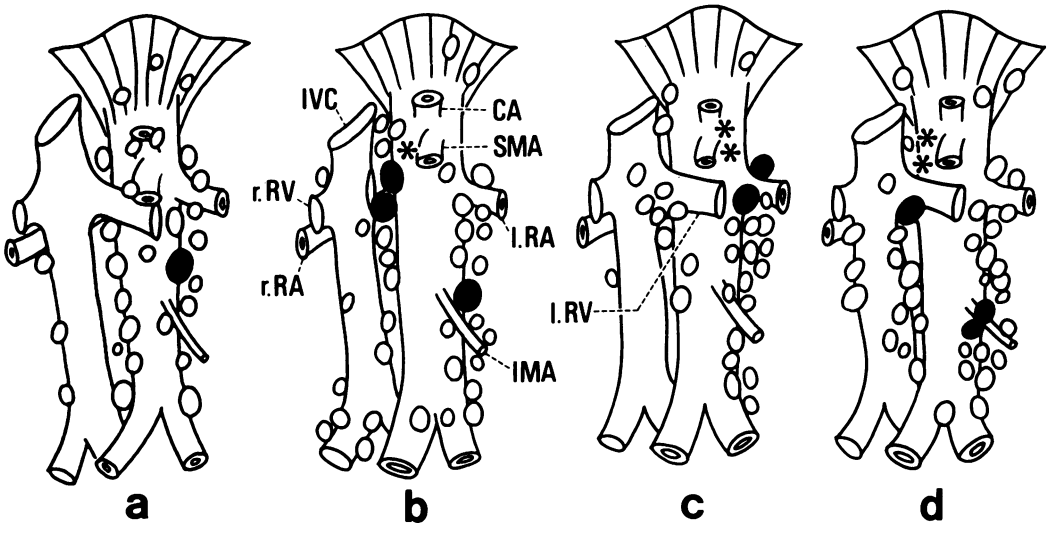
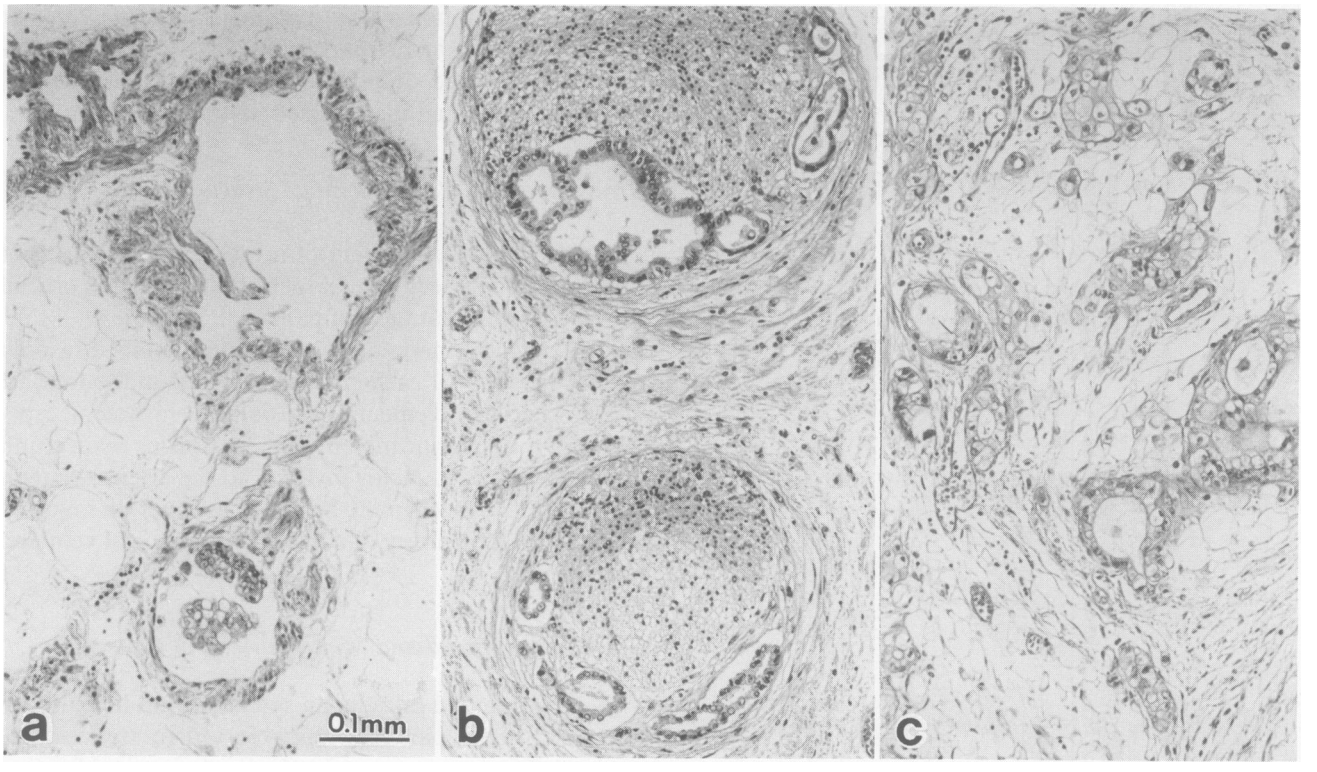


FIG. 3. Scheme of metastasis to para-aortic lymph nodes in four cases. Shaded circles represent positive nodes, and open circles are uninvolved nodes. Asterisks indicate "interstitial invasions." a. Case 1; b. Case 5; c. Case 7; d. Case 8. CA = celiac artery. IMA = inferior mesenteric artery. IVC = inferior vena cava. l.RA = left renal artery. l.RV = left renal vein. r.RA = right renal artery. r.RV = right renal vein. SMA = superior mesenteric artery.

Discussion

It is noteworthy that cases of pancreatic cancer with a small and macroscopically localized tumor tended to have fairly widespread extension of cancer cells through lymph node metastasis and infiltration within lymphatic vessels, nerves, and/or connective tissues as well as involvement of adjacent vascular structures. All these modes of spread plus intrapancreatic spread or multicentricity of cancer cells have been regarded as important factors in consideration of selection of therapy, surgical treatment, and assessment of prognosis in patients with pancreatic cancer. The present study has focused on these spread modes in relatively localized cancers of the pancreas.

Lymphatic metastasis of pancreatic cancer has been studied meticulously by Cubilla et al.[8] with the use of



FIGS. 4a–c. "Interstitial invasions" found in the surrounding tissues around the primary pancreatic tumor. H & E. *a.* lymphatic infiltration; *b.* nerve invasion; *c.* connective tissue invasion. *a–c:* same magnification.

Fortner's regional pancreatectomy specimens, most of which consisted of fairly advanced pancreatic cancers. They reported that 22 cases of duct cell adenocarcinoma of the pancreas, 21 of which were located in the head, often metastasized to the superior head (45%), posterior pancreaticoduodenal (45%), superior body (27%), and inferior head* (23%) lymph nodes groups. They did not have evidence of metastasis in the lymph nodes of the gastric, splenic, or common bile duct group. Other lymph node groups such as the inferior body, midcolic, pyloric, anterior pancreaticoduodenal, and mesenteric groups had involvement in 5–9% of their cases.

Thus, our results for the distribution and incidence of lymphatic metastases of T1 and T2 pancreatic cancer have shown a tendency similar to those of Cubilla. However, the following findings are especially noted in the present study:

(1) Metastases to the nodes of the inferior head group as defined by us were invariably found in all four cases of T2 cancer in the head of the pancreas.

(2) A few lymph nodes of the para-aortic group were found to have micrometastases in four of eight cases (50%), and distribution of the metastatic nodes ranged between the origin of the bilateral renal artery and that of the inferior mesenteric artery.

(3) Two of the four T1 tumors, both less than 1 cm in diameter, had no lymphatic metastasis.

(4) Mediastinal or cervical nodes were not involved in any case.

Anatomically, as our previous study has shown,[9] lymphatic vessels from the pancreas are closely related to the nodes of the inferior head group and para-aortic lymph nodes. Therefore, it is no wonder that the lymph nodes in the inferior head and para-aortic region were extremely vulnerable to metastasis from the cancer of the pancreas. However, lymphatic metastasis of pancreatic cancer to these regions has been mentioned little so far.[10,11] We should pay more attention to the inferior head and para-aortic lymph nodes when we consider metastasis from the cancer of the pancreas. Further studies would also be necessary for more accurate evaluation of the incidence of metastasis to other lymph node groups.

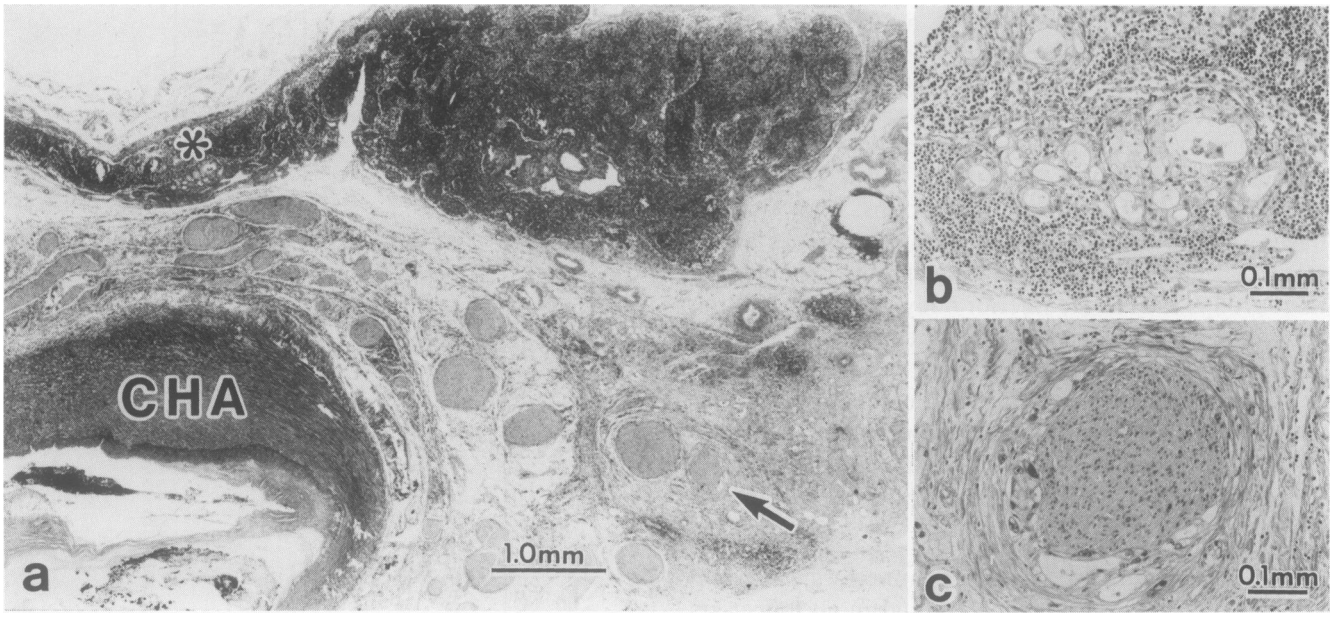
Lymphatic vessels, nerves, and loose connective tissues around the main tumors were involved in six, five, and eight of our eight cases, respectively. The range of lymphatic vessel, nerve, and connective tissue involvement by cancer cells was limited around the primary tumor of the pancreas and was almost the same as that of lymph

TABLE 3. *"Interstitial Invasion" of T1 and T2 Pancreatic Cancer*

Area*	Case No.	Peri-gastric	Anterior Pancreatico-duodenal	Posterior Pancreatico-duodenal	Superior Head	Superior Body	Inferior Head	Inferior Body	Splenic	Hepato-duodenal Ligament	Juxta-aortic	Para-aortic
T1	1	—	—	—	—	l2, n1, c1	—	—	—	—	—	—
	2	—	—	—	—	l1, n2, c1	—	—	—	—	—	—
	3	—	c1	—	—	—	—	—	—	—	—	—
	4	—	—	—	—	l1, n1, c1	—	—	—	—	—	—
T2	5	—	l2, c2	l2, c1	l1	—	—	—	—	—	l1	l1
	6	—	n3, c1	n3, c2	n3, c1	l1	c1	—	—	—	—	—
	7	—	c2	l2, n2, c2	l1, n3	l1, n1	l1, n2, c1	—	—	—	l1, n2, c1	l1
	8	c1	n2, c1	l1, n3, c2	—	—	n3, c1	—	—	—	n3, c1	n1

* The areas of "interstitial invasion" are the same as those of lymph node grouping used in Figure 2 and Table 2.
l = lymphatic vessel infiltration; n = nerve invasion; c = connective tissue invasion; — = no "interstitial invasion"; 1 = mild; 2 = moderate; 3 = marked.

* The inferior head group of Cubilla et al.[8] is probably a part of our inferior head group, which mainly represents lymph nodes in the radix of the mesentery, including the midcolic and jejunal groups of Cubilla et al.



FIGS. 5a–c. *a.* Cancer cells (arrow, magnified in *c*) found in the perineural space of the nerve plexus along the common hepatic artery (CHA) near an involved node (*, magnified in *b*) of superior head group. Case 6. H & E.

node metastasis, except in the para-aortic region. The high incidence of cancer spread through lymphatics and nerves suggests that wide resection of the peritumoral tissue and nerve plexuses should be required for complete eradication of cancer cells.

Although nerve invasion, especially perineural invasion, has been known to be closely related to the lymphatic system,[12] nerve involvement seems to be somewhat different from lymphatic involvement, as indicated by our results that these two modes of spread were not completely identical in their extent.

Direct invasion to the portal vein system was observed in four of our eight T1 and T2 tumors. Vulnerability of the portal vein system to cancer invasion has already been mentioned by many other authors.[1,13,14] On the other hand, direct invasion to the walls of major arteries was rarely encountered, despite the fact that cancer cells were frequently found in the tissues, especially nerve plexuses, around the arteries. These results might support to some extent the resection of major vein(s) of the portal system and periarterial tissues for a T2 pancreatic cancer.

There are many reports[15–17] that showed multifocal cancer lesions in the pancreas in approximately 20% of total pancreatectomy specimens. In our small number of cases, none had multiple foci of cancer in the pancreas or showed marked intraductal spread. Since one of the rationales of total pancreatectomy for pancreatic cancer, especially for that in the head of the pancreas, is based on the alleged high incidence of multicentricity and remarkable intraductal spread of cancer,[17] it is necessary to study many more specimens on universally accepted histological criteria. At least from our results, intrapancreatic spread or presence of intrapancreatic multifocal cancers seems to be less significant than extrapancreatic extension in patients with T1 and T2 primary tumor of the pancreas.

From our study, although it is composed of a small number of cases, it has been suggested that some of T1 and most of T2 pancreatic cancers have a rather extensive spread, such as para-aortic lymph node metastasis and major vascular involvement. This means that pancreatic cancer, even of small size and with macroscopically localized extension, has an extremely malignant nature, which results in a very low rate of long-term survival in patients with this disease. However, as demonstrated by our two T1 cases with primary tumors less than 1 cm in diameter, extremely small pancreatic cancers may have a limited extension, which is most likely to be resected with a chance for cure. In this respect, early diagnosis of pancreatic cancer is urgently needed.

TABLE 4. *Direct Invasion into Major Vascular Structures*

Case No.		SMV	SV	PV	SMA	CHA	MCA	SA
T1	1	—	—	—	—	—	—	—
	2	—	+	—	—	—	—	—
	3	—	—	—	—	—	—	—
	4	—	—	—	—	—	—	—
T2	5	—	—	—	—	—	—	—
	6	+++	—	+++	—	—	—	—
	7	+++	++	+++	—	—	+++	—
	8	+	—	+	—	—	—	—

— = no invasion. +–+++ = invasion up to the adventitia (+), media (++), and intima (+++).

SMV = superior mesenteric vein. SV = splenic vein. PV = portal vein. SMA = superior mesenteric artery. CHA = common hepatic artery. MCA = middle colic artery. SA = splenic artery.

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